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Cellular Aspects of Atopic Dermatitis

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Abstract Atopic dermatitis (AD) is a highly pruritic, chronic, and relapsing inflammatory skin disease. Recent interest in AD has been sparked by reports of its increasing prevalence and its contribution to increasing health care costs. A precise understanding of immunologic mechanisms is crucial for the development of effective treatment strategies for AD. Various studies reveal that AD has a multifactorial cause with the activation of complex immunologic and inflammatory pathways. This review will discuss cellular-mediated immunological pathomechanisms of AD. Emphasis will be given to the role played by T cells, antigen-presenting cells, eosinophils, and keratinocytes. We also examine the immunological effect of superantigens on various inflammatory cells including T regulatory cells.

Keywords Atopic dermatitis · T cell · Antigen-presenting cell · Eosinophil · Keratinocyte · Superantigens · T regulatory cell

Abbreviations

AD	atopic dermatitis
APC	antigen-presenting cell
LC	Langerhans' cell
GM-CSF	granulocyte–macrophage colony-stimulating factor
CLA	cutaneous lymphocyte-associated antigen
SAg	superantigen
DC	dendritic cell
FcεRI	high-affinity receptor for IgE
FcεRII	low-affinity receptor for IgE
IDEC	inflammatory dendritic epidermal cell
MCP	monocyte chemoattractant protein
TARC	thymus and activation-regulated chemokine
pDC	plasmacytoid dendritic cell
MBP	major basic protein
EPD	eosinophil peroxidase
ECP	eosinophil cationic protein
EDN	eosinophil-derived neurotoxin
LT	leukotriene
PAF	platelet-activating factor
MCP	monocyte chemotactic protein
TNF	tumor necrosis factor
Treg cell	T regulatory cell

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Atopic dermatitis (AD) is a highly pruritic, chronic, and relapsing inflammatory skin disease characterized by typically distributed eczematous skin lesions with lichenification, excoriations, severe dry skin, and susceptibility to cutaneous infections [1, 2]. AD commonly presents during early infancy and childhood, but it might persist into or start in adulthood [3]. Recent interest in AD has been sparked by reports of its increasing prevalence and the significant adverse effects of AD on patient's quality of life [4, 5]. In this review, we will discuss cellular-mediated immunological mechanisms of AD.

Immune Mechanisms

Compared to normal healthy controls, clinically unaffected skin in AD is not normal. It exhibits mild epidermal hyperplasia and a sparse perivascular T cell infiltrate [6].

Compared with normal nonatopic skin, AD unaffected skin demonstrate an increased number of Th2 cells expressing IL-4 and IL-13, but not IFN-γ, mRNA. Acute eczematous skin lesions are characterized by spongiosis of the epidermis and large numbers of antigen-presenting cells (APCs) binding IgE molecules on their surface [7]. There is a marked infiltration of activated memory T cells bearing CD3, CD4, and CD45RO [8]. Acute AD patients have significantly greater numbers of IL-4, IL-5, and IL-13 mRNA-expressing cells, but do not contain significant numbers of IFN-α or IL-12 mRNA expressing cells [6].

In chronic skin, lesions have strong lichenification with a hyperplastic epidermis and elongation of rete ridges. There is an increased number of IgE-bearing Langerhans' cells (LCs) in the epidermis, and macrophages dominate the dermal mononuclear cell infiltration [8]. Chronic AD skin lesions have significant fewer IL-4 and IL-13 mRNA expressing cell, but increased number of cells expressing IL-5, granulocyte–macrophage colony-stimulating factor (GM-CSF), IL-12, and IFN-α mRNA compared to acute AD. Recent studies suggest that IL-11 might involve the collagen deposition during chronic AD [9].

T cells

T lymphocytes play a prominent role in AD [10, 11]. Clinical studies have shown that T lymphocytes are most important cells in the pathogenesis of AD [12]. AD patients have increased levels of activated circulating T cells and increased levels of L-selectin and the secretory IL-2R, which are lymphocyte activation markers and which correlate with the disease severity [13–15]. The activation of T cells within the skin, and the subsequent release of cytokines and other effector molecules, results in clinically apparent T cell-mediated skin disease. Activated skin-homing T cells expressing the selective skin-homing receptor, cutaneous lymphocyte-associated antigen (CLA), induce IgE mainly via IL-13 and prolong eosinophil lifespan mainly via IL-5 [16, 17].

House dust mite allergen patch test can induce AD skin lesions with two phases: an initial phase with predominantly IL-4 producing Th2 cells and a subsequent phase after 24 to 48 h characterized by INF-γ producing Th1 cells [1]. The important role that Th1 and Th2 cytokines play in the skin inflammatory response has been demonstrated in experimental animal studies. IL-4 transgenic mice develop inflammatory pruritic skin lesions similar to AD, suggesting that Th2 cytokines play a critical role in AD [18]. In IL-5 knockout mice, the allergen-sensitized skin has been found to have no eosinophils and exhibits decreased thickening; skin from IL-4 knockout mice display normal thickening of the skin layers, but has a reduction in eosinophils. The skin of INF-γ knockout mice is characterized by reduced dermal thickening [19].

CLA defines the subset of skin-homing T cells that binds to E-selectin, and adhesion molecule expressed by endothelial cells in inflamed tissues during the first step of leukocyte extravasation [20, 21]. More than 80% of skin-infiltrating T lymphocyte express CLA molecule [22]. Superantigens (SAgs) can induce T cell expression of CLA antigen via stimulation of IL-12 production [23]. Intracellular cytokine staining revealed that CLA T cells contain high amounts of IL-13 and IL-5 but only small amount of IL-4 or INF-γ [16]. AD skin microenviroment components (IL-2, IL-4, IL-15, fibronectin, and collagen IV) can prolong the survival of T cells infiltrating the dermis and epidermis, and cause more-pronounced tissue damage and induce chronic eczema [24].

Activated T cell have been found to induce keratinocyte apoptosis, leading to the spongiotic process found in AD [25, 26]. This process is mediated by T cell-derived INF-γ which upregulates Fas (CD95) on keratinocyte. The lethal hit is delivered to keratinocytes by Fas-ligand expressed by skin-infiltrating T cells and soluble Fas-ligand released from T cells. Furthermore, keratinocytes undergoing apoptosis release INF-γ-induced chemokines (IP-10, Mig, and ITAC), which induces a second step of chemotoxis of CXCR3 bearing T cells toward the epidermis and might augment the skin inflammation and keratinocyte apoptosis [27].

Antigen-Presenting Cells

The immune response to foreign proteins is dependent on the efficiency and selectivity of antigen uptake by APCs. APCs play a key role in driving the inflammatory reaction in AD lesions [28]. APCs, like monocyte, LCs, and dendritic cells (DCs), express 3 different IgE-binding structures on their cell surface: the high-affinity receptor for IgE (FcεRI), the low-affinity receptor for IgE (FcεRII, CD23), and the IgE-binding lectin galectin-3 [29–31]. The expression of FcεRI and FcεRII on monocytes in the peripheral blood is increase in AD subjects. Compared to uninvolved skin, the lesional skin of AD patients contains an increased number of IgE-bearing LCs and inflammatory dendritic epidermal cells (IDEC), which express FcεRI [32]. But LCs at nonlesional sites still bear higher receptor numbers than nondiseased skin. Both cell types play a central role in the uptake and presentation of antigen to Th1 and Th2 cells [33]. The clinical importance of IgE-bearing LCs is supported by the observation that the presence of FcεRI- and IgE-bearing LCs is required to provoke eczematous

reaction after application of aeroallergens on the skin of patients with atopic disease [34].

Neither FcεRI$^+$ IDEC nor FcεRI$^+$ LC can be found in healthy skin [32], FcεRI expression on LC and IDEC may result from high serum IgE levels [35] and FcεRI expression on DC in the skin might mirror a systemic immunological response to atopic disease [36]. Recent studies demonstrated that IL-10 expression by APCs and T cells is critical for Th2 cell development in a murine model of AD [37]. In humans, FcεRI on APCs also play a pivotal role in modulating the differentiation. Crosslinking of FcεRI on APCs might induce the production of IL-10 and prevent their differentiation in DCs [38]. The high expression of FcεRI on LCs and IDECs in AD patients could be detected with a high sensitivity and specificity from other inflammatory skin diseases, and FcεRI/FcεRII ratio is used to distinguish between extrinsic and intrinsic AD [39, 40].

FcεRI activation of LCs leads to the release of chemokines, such as monocyte chemoattractant protein (MCP)1, IL-16, thymus- and activation-regulated chemokine (TARC), and macrophage-derived chemokine, which might recruit the other proinflammatory cells into the skin. It has been shown that LCs activated by FcεRI drive native T cells into IL-4 producing TH2 cells [41]. In addition, FcεRI-activated IDECs, like DCs, prime native T cells into INF-γ producing Th1 cells and release IL-12 and IL-18 [33]. After successful topical treatment of AD lesions, the number of IDECs in the epidermis decreases [35].

Plasmacytoid dendritic cells (pDCs), a second population of DC, can produce type-I interferons and play a central role in viral defense. In contrast to other inflammatory skin diseases, AD lesional sites contain very few pDC [42]. Furthermore, pDC of AD patients expressed high levels of FcεRI- and FcεRI-preactivated pDC produce less type-I interferons after stimulation with CpG motifs [43]. This might explain why the high susceptibility of AD patients to viral infections.

Eosinophil

Under physiological conditions, eosinophils are almost exclusively limited to the digestive tract [44, 45] and are not present in most other tissues. Blood eosinophilia is present in most patients of AD [46]. However, tissue eosinophilia has been shown to be a feature in AD and it also correlates with disease severity [47]. In a murine model of AD, tissue eosinophilia correlated with an increase in the thickness of the epidermal and dermal layers [19]. The level of circulating eosinophils correlates with disease activity and responses to therapy for AD [48].

The eosinophil contains several cationic granule proteins including major basic protein (MBP), eosinophil peroxidase (EPD), eosinophil cationic protein (ECP), and eosinophil-derived neurotoxin (EDN) [49]. They all increase microvascular permeability [50] and induce wheal-and-flare reaction in human skin [51]. The level of ECP in serum has been frequently used as the marker for monitoring AD activity [52, 53]. Besides ECP, serum EDN, MBP, and urine eosinophil protein X levels are also the markers for monitoring AD activity [54–56]. MBP and ECP were studied as markers of eosinophil degranulation of skin biopsy from AD. These eosinophil granule proteins are not only present inside eosinophil but also in the extracellular space [57]. The dominant MBP staining was localized in the upper dermis from AD lesions. In contrast, the specimen from unaffected skin showed only minimal extracellular MBP staining in the upper dermis. These findings demonstrated that eosinophil activity in AD is through deposition of granule products.

Activated eosinophils not only release granule proteins but also generate lipid mediators such as leukotriene (LT) C4 and platelet-activating factor (PAF). Both PAF and LTC4 increase vascular permeability [58, 59]. PAF can attract and activate leukocytes to areas of inflammation, and LTC4 stimulates smooth muscle contraction. IL-5 enhances eosinophilopoiesis and eosinophil release from the bone marrow [60]. IL-5 also enhances chemotaxis of eosinophils [61]. Besides IL-5, IL-3 and GM-CSF have also been shown to stimulate eosinophil production in the bone marrow [62]. IL-4 receptor has been identified on eosinophils and IL-4 can prime eosinophils to certain chemotatic stimuli [63]. In contrast, TGF-β1 inhibits eosinophil survival in a dose-dependent manner and can induce apoptosis of eosinophils [64]. IL-5 also might increase eotaxin-mediated chemotaxis. Eosinophils also play an important role in the switch of a Th2 cytokine pattern in acute lesions of AD toward a more Th1-like pattern in chronic AD [17, 20]. On the other hand, Th2 cytokines (IL-4, IL-13, IL-9) can promote eosinophilia by regulating local IL-5 and eotaxin synthesis and by suppressing INF-γ production [65].

Several members of the C–C chemokine are important chemotactic factors for eosinophils including eotaxin and RANTES [66–68]. Both eotaxin and RANTES are produced by dermal fibroblasts [69]. Both keratinocytes and fibroblasts from AD increase the production of RANTES [67, 70]. Eotaxin and monocyte chemotactic protein (MCP)-3 are important in the early recruitment of eosinophils [71, 72]. RANTES, MCP-5, and MIP-1α involve at later time points eosinophil recruitment [73]. Beside C–C chemokines, some CXC chemokines also can induce eosinophil chemotaxis like CXCL9, CXCL10, and CXCL12 [74]. CCR-3 is the principle receptor for

eosinophil attraction [75] and the major ligand for CCR-3 include eotaxin, RANTES, MCP-2, MCP-3, and MCP-4 in human [76].

Keratinocyte

Keratinocytes are the most abundant cell type of the epidermis. Epidermal keratinocyte actively participate in the pathogenesis of AD by producing a number of cytokines and chemokines [77, 78]. GM-CSF is readily produced by keratinocytes in response to autocrine IL-1α, tumor necrosis factor-α (TNF-α), and to the T cell-derived cytokines IFN-γ, IL-4, and IL-17 [79–81]. Supernatants from AD keratinocytes strongly stimulated PBMC proliferation in a GM-CSF-dependent manner [76] and GM-CSF enhanced monocyte survival in chronic AD [82]. Other than GM-CSF, AD keratinocytes release higher amounts of TNF-α, IL-1α, and IL-1 receptor antagonist after INF-γ stimulation [80].

Chronic AD skin lesions have significantly fewer IL-4 and IL-13 mRNA-expressing cells, but great numbers of IL-5, GM-CSF, IL-12, and INF-γ mRNA-expressing cells than acute AD [2]. After exposure to INF-γ, keratinocytes express on their surface the adhesion molecule intercellular adhesion molecule (ICAM-1), crucial for T cell retention in the epidermis [83]. Keratinocyte overresponse to INF-γ may serve as a further mechanism to enhance disease severity in AD. More than 80% of T cells infiltrating the skin lesions express the CLA molecule and CLA^+ T cells coexpress the CCR4 receptor, the ligand for TARC (CCL17), and MDC (CCL22) [84]. CCR4 is also preferentially expressed by Th2 lymphocytes [85]. Keratinocytes might contribute to the selective recruitment of $CCR4^+$ lymphocytes through the production of TARC [86]. RANTEs, and MCP-1, which attract both Th1 and Th2 cells, are expressed by infiltrating leukocytes but especially by keratinocyte in AD skin lesions [87]. In AD skin lesions, keratinocyte also might increase synthesis of eotaxin and MCP-4 to activate and attract eosinophils [88].

AD skin is also deficient in the production of keratinocyte derived antimicrobial peptides (α-defensins and cathelicidins) needed for host defense against bacteria, fungi, and viruses [89, 90]. Thus, once *S. aureus* binds to AD skin, inadequate local host defense allows the microbe to colonize and predispose patients to infection. Th2 cytokines might inhibit the expression of human α-defensin 2 [90], and human α-defensin 3 [91], thus providing a reason why antimicrobial peptide expression is low in AD skin. The lack of skin innate immune responses might increase the propensity of disseminated infectious with herpes simplex or vaccinia virus in AD [8]. Unless there is imminent danger of exposure to small-pox, small pox vaccination is contraindicated in patients with AD.

Superantigen and Inflammatory Cells

More than 90% of patients with AD have staphylococcus aureus colonization of their skin lesion [92, 93]. An important mechanism by which *S. aureus* contributes to skin inflammation is the secretion of toxin known as SAgs [94]. Epicutaneous sensitization with SAg might induce allergic inflammatory skin immune response that characterizes AD [95]. Most AD patients make specific IgE antibodies direct against staphylococcal SAgs, and these IgE antisuperantigens correlate with skin disease severity [95]. SAgs may stimulate marked activation of T cells and macrophages [96, 97]. SAgs bind directly, without antigen processing, to MHC class II molecules on APCs and trigger the potent activation of T cells through selected T cell receptor β (TCR-β) variable region elements [94]. In an analysis of the peripheral blood skin-homing CLA^+ T cells from AD patients colonized with superantigen-producing *S. aureus* and T cells in their skin lesions, it was found that a T cell receptor β chain expansion consistent with superantigenic stimulation had occurred [98, 99]. In animal studies, *S. arueus* binding was significantly greater at skin sites with Th2 as compared to Th1-medicated skin inflammation because of IL-4-induced expression of fibronectin [100, 101]. Basophils from AD patients with IgE antibodies directed to SAgs release histamine on exposure to the relevant SAg [96].

SAgs might induce corticosteroid resistance in human PBMCs [102]. Our recent study revealed that superantigen-induced corticosteroid resistance of human T cells occurs through the activation of the mitogen-activated protein kinase kinase/extracellular signal-regulated kinase (MEK-ERK) pathway [103].

$CD4^+CD25^+$ T regulatory (Treg) cells have been shown to inhibit the development of airway eosinophilia in animal models of asthma [104]. Patients with XLAAD/IPEX disease [105] specifically lack $CD4^+CD25^+$ Treg cells and have severe eczema, increased IgE levels and eosinophil counts, and food allergy. Our recent study revealed that SAgs have a great impact on the functional properties of $CD4^+CD25^+$ Treg cells in AD [106]. AD have significantly increased numbers of peripheral blood Treg cells with normal immunosuppressive activity. However, after SAg stimulation, $CD4^+CD25^+$ Treg cells are not anergic but respond to the stimulation. Furthermore, when Treg cells were mix with $CD4^+CD25^+$ T cells and stimulated with SAg, Treg cells lose their immunosuppressive activity. In our unpublished data, SAgs might induce GITR-ligand expression on monocyte to reverse Treg cell function and

SAgs also can subvert Treg cell function via the induction of IL-2 production from PBMC.

Conclusion

AD is a common skin disease that usually presents during early infancy and childhood. Its increasing incidence has attracted public interest in this disease during the last few years. Various studies indicate that AD has complex immunological and inflammatory pathways. AD is a biphasic inflammatory skin disease. Acute AD skin inflammation is associated with increased Th2 cells, but chronic AD results in the infiltration of inflammatory IDECs, macrophages, and eosinophils. Increasing IL-12 production by these various cell types results in the switch to a Th1-type cytokine milieu associated with increased IFN-γ expression. Blood circulating CLA^+ Th2 cells of AD patients result in elevated serum IgE via IL-13 and prolong eosinophil life span via IL-5. Increased levels of circulating eosinophils and eosinophil granule proteins in the sera and the urine of AD patients correlate with disease activity and decrease in response to therapy for AD. More than 80% of skin-infiltrating T lymphocyte express CLA molecule and SAgs can induce T cell expression of CLA antigen via stimulation of IL-12 production. Activated T cells may induce keratinocyte apoptosis and the process is mediated by T cell-derived IFN-γ, which upregulates Fas on keratinocytes. Keratinocytes undergoing apoptosis release INF-γ-induced chemokines that induces CXCR3 bearing T cells toward the epidermis and might augment the skin inflammation and keratinocyte apoptosis. FcεRI activation of LCs might release various chemokines to recruit the other proinflammatory cells into the skin. LCs activated by FcεRI may drive native T cells into IL-4 producing TH2 cells. In addition, FcεRI-activated IDECs, like DCs, prime native T cells into INF-γ-producing Th1 cells and release IL-12 and IL-18. More than 90% of patients with AD have *S. aureus* colonization of their skin lesion. *S. aureus* may release SAg and it may stimulate marked activation of T cells and macrophages. AD have significantly increased numbers of peripheral blood $CD4^+CD25^+$ Treg cells with normal immunosuppressive activity. After SAg stimulation, Treg cells lose their immunosuppressive activity suggesting that Treg cells may not be functioning at the local skin level in AD colonized with SAg-producing *S. aureus*.

SAgs might induce GITR-ligand expression on monocyte to reverse Treg cell function and SAgs also can subvert Treg cell function via the induction of IL-2 production from PBMC.

Despite intensive research and significant progress in AD study, a unifying pathogenetic concept of AD has not been established. Future approaches in clinically and basic-oriented research will be needed to complete our understanding of this complex disease. It is hoped that this will provide us with the ability to develop effective therapeutic strategies and prevention mechanisms for AD.

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